OPINIONS

Topological indices

It is 25 years ago that connectivity indices and other topological indices emerged as alternative descriptors for structure-property-activity studies. While well received in some QSAR circles apparently they have not been welcome among some chemometricians. A recent paper by Lahana and coworkers (Computer Assisted Rational Design of Immunosuppressive Compounds, G. Grassy, B. Calas, A. Yasri, R. Lahana,* J. Woo, S. Iyer, M. Kaczorek, R. Floc'h and R. Buelow, Nature Biotechnology, 1998, vol. 16, pp. 748-752) calls for revision of reservations and re-evaluation of such skepticism. The authors describe a rational design of immunosupressive peptides without relying on information regarding their receptors or mechanism of action. The design strategy uses a variety of topological and shape descriptors in combination with an analysis of molecular dynamic trajectories for the identification of potential drug candidates. The researches started from 27 descriptors such as molecular volume, lipophilicity, 12 topological indices including Kier's kappa indices, Balaban index, Wiener index, Randic index (the connectivity index), Kier and Hall valence connectivity indices, Hall E-state sum, and a number of indicator variables (number of C atoms, H atoms, methyl groups, amino groups). Among the 13 selected descriptors four were topological indices. The strategy is based on the design and screening of virtual combinatorial libraries using rules derived from a comprehensive description of active and inactive molecules in a relevant learning set. This strategy allows the development of potential candidates without relying on the 3-D structure of the target receptor. The predictive capabilities of this kind of approach are improved using several filters, defined by the range of variation of a given descriptor for all known active compounds when compared to the range of variation of the same descriptor for all known inactive compounds.

A virtual combinatorial library was generated for the peptides of general form: RXXXRXXXXY, with seven variable positions in order to create the combinatorial library. Use of 35 amino acids (20 natural and 15 non-natural ones) leads to 357 combination (64 billion compounds), well above computing capacity. This number was reduced to 67 (almost 280,000 compounds) by taking into account lipophilicity

distribution (considered critical for the activity considered). The selected amino acids were V, I, T, W, G and nL (Nor-Leucin) The lead compounds were peptides, derived from the heavy chain of HLA class I, that modulate immune responses in vitro and in vivo. The lead peptide prolonged skin and heart allograft survival in mice. The learning set consisted of 19 peptides based on the above lead peptide, of which nine prolonged heart allograft survival in mice and ten had no significant effect. Rapid computation using the 13 selected molecular descriptors reduced the virtual library to 26 peptides that satisfied all the constraints. More elaborate calculations then allowed a comparison of the conformational space occupied by active and inactive peptides from the original learning set resulting in the selection of five peptides which were synthesized and tested in vivo.

The biological activity of peptide therapy with the rationally designed peptides has shown that four out of the five resulted in significant prolongation of allograft survival. The molecule predicted to be most potent displayed an immunosuppresive activity approximately 100 times higher than the lead compound.

This work illustrates a new avenue for using topological indices in rational design of biologically active compounds. It is worth pointing out (1) that no alternative computational approaches are today practical for combinatorial libraries having in excess of 100,000 compounds; (2) that topological indices along with other molecular descriptors apparently are highly efficient (in filtering two dozen compounds out of over quarter of million); and (3) that the resulting active compound was two orders of magnitude more potent than the lead compound. It may be argued that the paper of Lahana and coworkers represents historic step in QSAR and rational drug design and will be recognized as such.

Milan Randic,

Department of Mathematics and Computer Science,, Drake University, Des Moines, IA 50311